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Innovations

Speedel Staunches the Renin Cascade at Its Source

Hypertension gives no warning signs. Left untreated, it can lead to kidney and heart disease, retinal damage, and stroke. Its root causes are mostly unknown. About 190 million people in developed countries suffer from hypertension. The American Heart Association estimates nearly one in three U.S. adults have high blood pressure and that over a third of them do not effectively control it.

One of the key regulators of blood pressure is the renin angiotensin system (RAS). The RAS cascade is initiated by renin, a protease produced by the kidneys that cleaves the peptide angiotensinogen, converting it to angiotensin I. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE), which spurs blood vessels to contract and increases vascular resistance, raising blood pressure. Blocking either the formation or the action of angiotensin II is considered to be an effective way to control hypertension.

The existence of the renin pathway was first theorized in 1898 by Robert Tiegerstedt, a physiologist at the Karolinska Institute who experimented on rabbit kidneys. Renin catalyses the rate-limiting (or bottleneck) step of the RAS chain [1], so renin inhibitors stop the cascade cold. "The advantage of blocking the biological pathway at the very beginning is that there is no downstream molecule interfering with anything," said Dr. Jessica Mann, medical director at Speedel (http://www.speedel.com) a Swiss biotech company. Speedel, in conjunction with Novartis, will be the first to produce a new oral renin-inhibiting antihypertensive drug, SPP100, or aliskiren.

"Basically, when you treat hypertension, the only thing you treat is a couple of figures," said Mann. "And you want those figures to reach a magic number." (The definition of hypertension is 140/90 Hg [systolic/diastolic]) Mann added, "People don't die of high blood pressure on its own. People die of the long-term effects of high blood pressure on their hearts, their kidneys, and their brains." According to Mann, despite great interest in renin inhibitors, pharmaceutical companies virtually abandoned them in the 1990s because they were large, complicated molecules, expensive to produce, and their bioavailability and potency were too low to be effective.

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The Pit Viper Effect

The dangers associated with hypertension were recognized in the 1930s, but the first effective oral antihypertensive agents, diuretics, only appeared in the 1950s. Diuretics reduce blood pressure, in part, by increasing renal sodium excretion, thereby reducing the overall fluid volume in the body. They are still used today, both as first-line therapies and in combination with other drugs. Beta blockers were introduced in the 1970s, and calcium channel blockers in the 1980s. Beta blockers lower blood pressure by reducing the heart's overall blood pumping capacity; they also decrease renin release from the kidney. Angiotensin-converting enzyme (ACE) inhibitors were developed in the mid 70s, as an indirect result of earlier experiments on the blood pressure-lowering effects of Brazilian pit viper venom. The first orally active ACE inhibitor, captopril, was approved by the FDA in 1981. Calcium channel blockers and ACE inhibitors both reduce blood pressure through their vasodilatory effects.

Angiotensin receptor type II blockers (ARBs) were first marketed in the U.S. in the mid 90s. ARBs inhibit the vasopressive effects of angiotensin II, the principal mediator of RAS downstream of renin production, by selectively blocking the AT_1 receptors on the surface of target cells. By interfering with feedback inhibition, they increase angiotensin II levels. All or most of the deleterious effects of angiotensin II stimulation are mediated through the AT_1 receptor. In most patients, a single antihypertensive agent does not succeed in reducing blood pressure to target levels, so various drug combinations are used, often including a low-dose diuretic. The side effects of antihypertensive agents vary: ARBs have the fewest side effects and, in most studies, exhibit a placebo-like tolerability profile.

Call Back When the Molecule Shapes Up

Speedel, now numbering over 70 employees, was founded in 1998 as an indirect result of the merger between Ciba-Geigy and Sandoz that formed Novartis. Dr. Alice Huxley was in charge of the early development of aliskiren at Ciba-Geigy, but the Novartis management decided to discard the compound, primarily because of its high cost of manufacturing. Novartis had other hypertension candidates at the time, including Diovan (valsartan). In 1999, Huxley and her colleagues licensed aliskiren under a "call back option," meaning that if it successfully passed Phase II trials, Novartis would license it back for Phase III tests and commercialization.

"The synthesis of aliskiren was a major issue," said Dr. Peter Herold, director of chemistry at Speedel, whose team did extensive molecular modeling and crystallographic structure analysis to optimize the drug. "Aliskiren has four chiral centers in the molecule. Mathematically, you have 16 possibilities. From

a structural point of view, at the end of the day, only one is the one you want, as the others don't fit in the enzyme."

Aliskiren was licensed back by Novartis in 2002 and is commercialized under the trade name Tekturna. Novartis recently announced favorable phase III data covering over 7000 patients with mild-to-moderate hypertension in the U.S., E.U. and Japan who were treated for a period between 6 and 52 weeks. Aliskiren was also tested in conjunction with a diuretic (HCTZ), a calcium channel blocker (amlodipine), and an ACE inhibitor (ramipril). The FDA accepted aliskiren for regulatory review in April 2006.

"The data, at least what I've seen of it, looks pretty clean," said Dr. Alan Gradman, chief, division of cardiovascular diseases, the Western Pennsylvania Hospital, who was involved with some of the aliskiren clinical studies. According to Gradman, aliskiren lowers blood pressure and has a comparable side effect profile to an ARB. "It is not just about the hypertension and hemodyamics, it is also about inhibiting end organ damage effects that occur with arteriosclerosis and left ventricular hypertrophy and so on," said Gradman, "At this point in time there is very little data on the effects of aliskiren on any of these end organ effects. And part of the problem is that you cannot really study this well in animal models as the compound is very specific for human renin. What is interesting about renin inhibitors is that they antagonize the renin angiotensin system through a different pharmacologic mechanism than ACEs and ARBs, so the question is what effect they will have on the end points?"

Speedel says that aliskiren, unlike ACE inhibitors and ARBs, inhibits renin, i.e., plasma renin activity (PRA), a surrogate marker for heart attacks and kidney disease. Gradman pointed out that Novartis is now testing intermediate end points such as proteinuria (protein in the urine) to see if aliskiren attenuates the progression of kidney disease in patients. Novartis is also looking at LVH regression (left ventricular hypertrophy, the thickening of the heart muscle that occurs as a result of the heart having to contract against higher pressures) for cardiovascular disease, but it will be difficult to see results without specific trials measuring actual disease progression as an endpoint. Novartis is also hypothesizing that combining aliskiren with an ARB might provide long-term organ protection because there is no activation of RAS.

Speedel's inaugural strategy was to license promising cardiovascular or metabolic drug candidates from other companies, improve them, and then license them back to pharma. However, around 2002, Speedel started their own internal development program, Speedel Experimenta, now comprising 40 people. Speedel financed itself by raising U.S. $64 million through a sale of 500,000 treasury shares in March 2006. The company previously raised U.S. $183 million from private placements and two rounds of equity financing. Milestone revenues have totaled U.S. $44 million so far. Speedel is traded on the Swiss stock exchange.

Aside from aliskiren, Speedel has three other classes of renin inhibitors: the 600 series in-licensed from Roche; the 800 series, stemming from a collaboration with Locus Pharmaceuticals, now in preclinical testing; and the 1100 series, developed internally. Speedel is also developing SPP301, an endothelin A receptor antagonist for diabetic neuropathy that is in Phase III trials, and SPP200, an anticlotting agent licensed from Abbott for vascular graft occlusion, now in Phase II trials.

Renin Inhibitors Take Off

Speedel faces competition from rival Swiss company, Actelion (http://www.actelion.com) working with Merck on a renin inhibitor that entered human clinical trials in July 2006. "Aliskiren is still a substrate peptidomimetic, whereas Actelion's compounds are nonsubstrate analogs based on templates found originally by random screening." said Walter Fischli, Ph.D., head, drug discovery, biochemistry, and molecular biology at Actelion, "Before Actelion's breakthrough, pharmaceutical companies large and small failed to turn peptidomimetics into highly bioavailable renin inhibitors. The implications of low bioavailable compounds are usually high doses and variable pharmacologic results, with the ultimate question [being] whether a full blockade of the system can be achieved at all."

Vitae Pharmaceuticals, (http://www.vitaepharma.com), a private company based in Fort Washington, PA, also has a renin inhibitor in preclinical development for hypertension in conjunction with GlaxoSmithKline. The published literature on renin inhibitors contains contributions from other interested pharmaceutical companies, including Pfizer.

"Most of the renin inhibitors developed over the past two decades were large molecules and couldn't get through the GI tract," said Dr. Randall Zusman, director of hypertension and vascular medicine at Massachusetts General Hospital. "Aliskiren is a complex molecule, but it has sufficient bioavailability to inhibit renin activity in vivo, in doses that do not induce adverse side effects. Clinicians will be comparing these new drugs principally to ACE inhibitors and ARBs. Is this new strategy more effective than what we have available, with fewer side effects? A point in renin inhibitor-based drugs' favor is that they have a very long half life (aliskiren lasts approximately 40 hr). But until they are used by a larger number of patients, we don't really know a whole lot. The promise of this drug is to disrupt the [renin] cascade very early and be very complete in its inhibitory effect."

A century after Tiegerstadt ground up rabbit kidneys and identified RAS, treating hypertension, though considerably progressed, is far from perfected. Time will tell whether renin inhibitors fulfill their promise, but as people age and waistlines spread, increasing cardiovascular and metabolic diseases are sure to maintain the flow of demand for new drugs.

Selected Reading

1. Fisher, N.D., and Hollenberg, N.K. (2005). Renin inhibition: What are the therapeutic opportunities? J. Am. Soc. Nephrol. *16*, 592–599.

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